UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,827	09/05/2003	Martin Geppert	01269.US1	7147

25533 7590 06/30/2006

PHARMACIA & UPJOHN
7000 Portage Road
KZO-300-104
KALAMAZOO, MI 49001

EXAMINER
SHIN, DANA H

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,827	GEPPERT, MARTIN	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-10-04 & 6-18-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and by dependency, claims 2-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 at lines 3-7 recites "extending a population of random oligonucleotide RNAi progenitors comprising a fixed primer sequence; a random oligonucleotide sequence; and a fixed stem-loop structure;" . This claim language is vague and indefinite because the wording and construction of this particular portion of claim 1 taken as a whole indicates that each of the fixed primer sequence, the random oligonucleotide sequence, and the fixed stem-loop structure, as an independent, separate, and individual entity, constitutes a population of random oligonucleotide RNAi progenitors. This is internally inconsistent because each of the three elements recited at lines 5-7 must not be separate entities but be ligated to one another in a linear fashion as Figures 2-4 in order for the instantly claimed invention to work. Therefore, claims 1-11 have failed to distinctly claim the subject matter of the instantly claimed invention.

Claim 1 at line 7 recites " a fixed stem-loop structure". This claim language is vague and indefinite because a fixed, self-folded stem-loop structure cannot be maintained in a polymerase extension reaction which involves denaturing steps, although it is feasible for a fixed stem-loop sequence to be maintained (see Figures 3 and 4).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Rossi et al. (US 2004/0091918 A1).

Claims 1-5 and 11 are directed to a method to generate a population of inhibitor sequences ready for cloning by extending a population of random oligonucleotide RNAi progenitors with a fixed primer sequence, a random oligonucleotide sequence, and a fixed stem-loop structure via a polymerase extension reaction to create a double stranded product (claim 1), wherein said product is inserted into an expression vector (claim 2), wherein said expression vector is introduced into a cell (claim 3), wherein said cell is assessed for a phenotype (claim 4), and wherein the final random oligonucleotide product is 21 to 23 bases in length (claim 11).

Rossi et al. disclose a polymerase chain reaction (PCR)-based method of creating a hairpin RNA expression cassette by extending an RNAi template sequence with a fixed 5' oligonucleotide primer complementary to 29 nucleotides at the 5' end of the U6 promoter, a fixed 3' primer sequence complementary to 20 nucleotides at the 3' end of the U6 promoter, and a fixed 9-base loop (UUUGUGUAG) sequence to create a double stranded hairpin RNA

expression cassette, wherein the final hairpin RNA target sequence consists of 21 to 23 bases in length (paragraphs 0004 and 0038). This final product is then transfected into a 293 cell line, resulting in the inhibition of HIV-1 rev-EGFP expression, which inherently indicates a loss of function of HIV-1 rev-EGFP in 293 cells. They teach that this PCR-based hairpin RNA expression cassette synthesis can be utilized for endogenous targets when there is a positive selection or a FACS sortable phenotype available (paragraph 0075). They further teach that this procedure can be utilized for the rapid screening and testing of randomized siRNA encoding genes to identify functional siRNAs or for screening siRNA gene libraries. Accordingly, all the limitations are met by Rossi et al. for instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossi et al. as applied to claims 1-5 and 11 for §102 rejections above, and further in view of Fraser et al. (*Nature,* 2000, applicant's citation No. BE, PTO Form 1449 filed on May 10, 2004).

Claims 1-11 are drawn to a method to generate a population of inhibitor sequences ready for cloning, wherein a cell transfected with the inhibitor sequences is assessed for a phenotype caused by partial loss of function of a receptor gene.

Rossi et al., as described above, teach a method of generating hairpin RNAi expression cassettes via a polymerase extension reaction method, which results in gene expression inhibition when transfected into a cell. They teach that this particular method of generating hairpin RNAi is inexpensive and rapid compared to traditional chemical synthesis of short double stranded RNAs (paragraph 0011). They also teach that the final oligonucleotide of hairpin RNAi is 21 to 23 based in length, which falls under the limitations of 15 to 50 bases in length (claim 9) and 20 to 30 bases in length (claim 10). They do not teach assessment of phenotypes caused by partial loss of function of a receptor gene.

Fraser et al. teach a method of comprehensive, high-throughput genomic analysis of *C. elegans* chromosome I by making a library of double stranded RNA-expressing bacteria corresponding to genes on chromosome I, followed by systematic investigation of loss-of-function phenotypes. Specifically, they teach a gene locus "mom-5", which is identified to be a frizzled-like gene, a receptor gene for Wnt-signaling proteins. They teach that the *C. elegans* with mom-5 locus targeted by RNAi display both "Uncoordinated" (Unc) and weak embryonic lethality phenotype while unaffected with developmental delay phenotype (see Table 3 on page 326). Fraser et al. further teach that RNAi may result in partial loss of gene function, thus does not accurately reflect the null phenotypes of all genes. They teach that the library of RNAi and RNAi-based genetic screens can be used to screen the entire genome for genes involved in a particular process and may be used to identify complete or partial loss-of-function phenotypes, which will be a useful tool for reverse genetics (page 329).

It would have been obvious to one of ordinary skill in the art at the time of instantly claimed invention to use the PCR-based method of siRNA synthesis of Rossi et al. and apply

such method to the high-throughput genomic analysis of an organism for complete or partial loss-of-function phenotype studies as taught by Fraser et al. One of ordinary skill in the art would have been motivated to combine the teachings of Rossi et al. and Fraser et al. in order to generate transfectable RNAi progenitors with reduced cost and increased speed because Rossi et al. teach that their method of making RNAi progenitors is more cost-effective and rapid than the conventional chemical synthesis of RNAi progenitors, which can be transfected into cells and assessed for phenotypes, thereby allowing the skilled artisan to identify the target sequence with the observed phenotype in a large, comprehensive scale of genomic screening and analysis, as suggested by Fraser et al. The skilled artisan would have practiced the combined teachings of the prior art with a reasonable expectation of success because the RNAi construct has been demonstrated to be transfected into mammalian cells with successful gene inhibition by Rossi et al. and a library of RNAi sequences and its application to reverse genetics, which primarily uses assessment of mutant phenotypes and a known gene sequence, has been successfully demonstrated in *C. elegans* by Fraser et al. Accordingly, instantly claimed invention taken as a whole is *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

dhs
June 22, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER